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Attention Problems, Inhibitory Control, and Intelligence Index Overlapping Genetic Factors: A Study in 9-, 12-, and 18-Year-Old Twins

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It is assumed that attention problems (AP) are related to impaired executive functioning. We investigated the association between AP and inhibitory control and tested to what extent the association was due to genetic factors shared with IQ. Data were available from 3 independent samples of 9-, 12-, and 18-year-old twins and their siblings (1,209 participants). AP were assessed with checklists completed by multiple informants. Inhibitory control was measured with the Stroop Color Word Task (Stroop, 1935), and IQ with the Wechsler Intelligence Scale for Children (Wechsler et al., 2002) or Wechsler Adult Intelligence Scale (Wechsler, 1997). AP and inhibitory control were only correlated in the 12-year-old cohort ($r = .18$), but appeared non-significant after controlling for IQ. Significant correlations existed between AP and IQ in 9- and 12-year olds ($r = -.26$/–.34). Inhibitory control and IQ were correlated in all cohorts ($r = -.16$, $-.24$ and $-.35$, respectively). Genetic factors that influenced IQ also influenced inhibitory control. We conclude that the association between AP and inhibitory control as reported in the literature may largely derive from genetic factors that are shared with IQ.

Keywords: attention deficit, IQ, inhibition, childhood, endophenotype

Children with attention deficit/hyperactive disorder (ADHD) are characterized by inattentive, impulsive, and hyperactive behavior. ADHD has a great impact on affected families in terms of academic, social, and behavioral dysfunction (Mannuzza & Klein, 2000; Mannuzza, Klein, Abikoff, & Moulton, 2004) and is at the moment the most common neuro-developmental disorder of childhood with 5% of children worldwide affected (Polanczyck, De Lima, Horta, Biederman & Rohde, 2007). It has been hypothesized that inattentive, impulsive, and hyperactive behaviors (summarized as attention problems (AP) in this paper) are normally distributed in the population with ADHD positioned at the extreme (problem) tail of the distribution (Kuntsi, Andreou, Ma, Borger, & van der Meere, 2005; Levy, Hay, McStephen, Wood, & Waldman, 1997). Hay, Bennett, Levy, Sergeant, and Swanson (2006) and Polderman, Derks, et al. (2007) demonstrated with an AP scale measuring the continuum of AP (i.e., strengths and weaknesses) that the scores of general population samples indeed showed a normal distribution.

In the past decade many studies have investigated the origins, characteristics, and related disorders of ADHD and AP in clinical and normal population samples. Early studies revealed that AP runs in families (Biederman et al., 1992), and twin registers have proven to be a valuable source of information to investigate the etiology of the familial clustering. For example studies of The Netherlands Twin Register showed in large samples of twins that AP are stable during childhood (Rietveld, Hudziak, Bartels, van Beijsterveldt, & Boomsma, 2004), and highly heritable (~75%) between age 3 and 12 years (Rietveld, Hudziak, Bartels, van Beijsterveldt, & Boomsma, 2003). Boys tend to have more AP than girls but Derks, Dolan, Hudziak, Neale, and Boomsma (2007); Derks, Hudziak, van Beijsterveldt, Dolan, and Boomsma (2004); Hudziak, Derks, Althoff, Rettew, and Boomsma (2005);

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and Rietveld et al. (2003) demonstrated that genetic influences on AP are equally important for boys and girls. AP are often assessed with behavior questionnaires that can be completed by different informants. Mother and teacher ratings of AP show overlap but also specificity (Derks, Hudziak, van Beijsterveldt, Dolan, & Boomsma, 2006; Simonoff et al., 1998). Thus, there is a common phenotype of AP on which mothers and teachers agree, but there are also situation and rater specific phenotypes. In a recent study Derks et al. (2008) investigated the presence of an underlying "AP/ADHD" construct that was shared between questionnaire data and the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., [*DSM–IV]*; American Psychiatric Association, 1994) based diagnostic interview data. The results showed high heritabilities for all instruments, and a large genetic overlap between questionnaire ratings and *DSM–IV* diagnoses of ADHD, suggesting that the detection of genes for ADHD could be based on (less time and money consuming) questionnaire scores rather than diagnostic interviews.

Over time evidence has accumulated that symptoms of AP are related to impairment in the prefrontal cortex and the subcortical cortices that project to it (Casey & Durston, 2006; Castellanos & Tannock, 2002; Shaw et al., 2006; van't Ent et al., 2007), and it may be that genetic effects on prefrontal brain function have an important contribution to the robust heritability of AP. The prefrontal cortex is one of the crucial brain regions for executive functioning (Carpenter, Just, & Reichle, 2000; Fuster, 1997; Hampson, Driesen, Skudlarski, Gore, & Constable, 2006; Prabhakaran, Narayanan, Zhao, & Gabrieli, 2000; Smith & Jonides, 1999) and measures of executive functioning have been proposed as promising endophenotypes (i.e., underlying genetic biomarkers) for AP. Several studies reported impairment of executive functioning in children with ADHD (Barkley, 1997; Bidwell, Willcutt, DeFries, & Pennington, 2007; Manly et al., 2001; Pennington & Ozonoff, 1996; Slaats-Willemse, Swaab-Barneveld, de Sonneville, Van der Meulen, & Buitelaar, 2003; Swaab-Barneveld et al., 2000; Swanson, 2003; Stins et al., 2005; Tannock, 1998). A meta-analysis by Willcutt, Doyle, Nigg, Faraone, and Pennington (2005) showed that especially inhibition, working memory, planning, and vigilance were impaired. Others, however, have increasingly questioned the central role of deficits in executive functions in ADHD (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Huang-Pollock, Nigg, & Carr, 2005; Jonsdottir, Bouma, Sergeant, & Scherder, 2006; Mason, Humphreys, & Kent, 2003). For instance, Stroop interference, a core measure of inhibitory control that has long been regarded to be the most prominent deficit in children with AP (Barkley, 1997; Brocki, Nyberg, Thorell, & Bohlin, 2007; Friedman et al., 2007; Nigg, 1999, 2001; Rommelse et al., 2008) proved not to be significantly associated to ADHD in a meta-analysis of 17 independent studies by Van Mourik, Oosterlaan, and Sergeant (2005).

Unfortunately, most of the studies have focused on the phenotypic association between executive function and AP, and only very few have examined their genetic association. Only the latter association, however, directly tests the possibility that genetic effects on prefrontal brain function contribute to the heritability of AP. To date, studies on the genetics of executive functioning are scarce (for an overview, see Doyle et al., 2005), and studies in children are especially limited. Polderman, Posthuma, et al. (2007) investigated the genetic background of working memory, selective and sustained attention using a longitudinal design. In young children (age 5 years) the heritability estimates of these executive functions ranged between 28 and 59%, and in older children (age 12) between 42 and 73%; the stability over time was due to genetic factors only. At age 5, Polderman, Gosso, et al. (2006) also tested whether the association between AP and executive functioning is attributable to common etiologic influences. The genetic correlations of working memory, selective and sustained attention with AP as rated by the teacher ranged between −0.31 and −0.38, but the genetic correlations with maternal ratings of AP were nonsignificant. Various inhibitory control tasks have also been used. Groot, de Sonneville, Stins, and Boomsma (2004) reported a heritability of 54% for reaction time measures on a computerized Go–No go task, in a 5-year-old Dutch twin sample (237 twin pairs). For inhibitory control, measured as accuracy in this task, no heritability was present. In a smaller Dutch sample (145, 12-year-old twin pairs), inhibitory control was measured with the Stroop Color Word (Stroop, 1935) task and the Eriksen Flanker task (Eriksen & Eriksen, 1974). For Stroop interference the heritability was estimated at 49%. Inhibitory control assessed with the Eriksen Flanker showed no genetic influences (Stins, van Baal, Polderman, Verhulst, & Boomsma, 2004). The genetic correlation between inhibitory control and AP has not been assessed so far.

In testing the association between executive functioning, including inhibitory control, and AP, some studies have attempted to correct for IQ because IQ is related to both AP and executive functioning. This association may derive from shared genetic factors because significant genetic correlations have been reported between IQ performance and AP (Friedman et al., 2007; Kuntsi et al., 2004; Polderman, Gosso, et al., 2006), and between IQ performance and executive functions (Polderman, Gosso, et al., 2006; Polderman, Stins, et al., 2006). It is currently unclear whether there are genetic factors that are specific to AP and executive functioning, or whether these factors completely overlap with those influencing IQ.

Summarizing the results of our prior work in Dutch twins (see Table 1) and related findings in the literature we conclude that—irrespective of age, sex, or method of rating: (a) ADHD and AP are highly heritable during childhood; (b) executive functions, including inhibitory control, during childhood are also heritable, but to a lesser extent; (c) there is some evidence of a genetic correlation between AP and executive functioning, giving the impression that children who are genetically vulnerable for deficits in executive functioning may also have higher risks for AP; and (d) the genetic correlations between IQ, AP, and executive functioning remain to be established.

The first objective of the current study was to examine the relation between AP and inhibitory control at different moments during childhood. The second objective was to test to what extent the genetic factors influencing IQ, AP, and inhibitory control overlap, and whether there is a set of genetic factors independent of IQ that affects AP and inhibitory control only. Identification of the genetics factors shared by AP and inhibitory control but not by general cognitive ability could help reveal the specific role of inhibitory control in the pathophysiology of AP. We used the data from three independent cohorts of twins of different ages, namely 9-year-old, 12-year

Table 1
Overview of Genetic Studies by The Netherlands Twin Register (NTR) on AP, ADHD, and Executive Functions

Study	Age, sample *N*, and cohorts NTR	Instruments	Results
Genetic studies on AP and ADHD			
Rietveld et al. (2004)	3 (n = 11,938 twins), cohorts 86–93; 7 (n = 10,657 twins), cohorts 86–93; 10 (n = 6,192 twins), cohorts 86–91; 12 (n = 3,124 twins), cohorts 86–89	CBCL: AP scale mother	h^2 ~ 75% at each age; association over time due to genetic factors
Hudziak, Derks, Althoff, Rettew, & Boomsma, (2005)	7 (1,595 twin pairs), cohorts 92–96	Conners: ADHD index mother	h^2 78%
Derks, Hudziak, van Beijsterveldt, Dolan, & Boomsma (2004)	3 (n = 9,689 twin pairs), cohorts 86–97	CBCL: AP scale mother and father	h^2 ~78%
Derks, Hudziak, van Beijsterveldt, Dolan, & Boomsma (2006)	7 (n = 2,259 twin pairs), cohorts 92–96; 7 (n = 2,057 twin pairs), cohorts 92–96	TRF: AP scale teacher; CBCL: AP scale mother	h^2 common factor 32%, specifics 45% (M) and 23% (T)
Derks, Dolan, Hudziak, Neale, & Boomsma, (2007)	7 (n = 1,651 twins), cohorts 92–96	Conners: subscales teacher	h^2 56–71%
Derks et al. (2008)	7 (n = 10,018 twins), 10 (n = 6,565 twins), 12 (n = 5,780 twins) 12 (n = 4,887 twins); 12 (n = 1,006 twins), cohorts 89–94	CBCL: AP scale mother; Conners: ADHD index mother; *DSM*interview: ADHD syndrome	h^2 *DSM* 65%; h^2 Conners 84%; h^2 CBCL 75% large genetic overlap among instruments
Polderman, Posthuma, et al. (2006)	5 (n = 237 twin pairs), cohorts 90–92	TRF: AP scale teacher	h^2 63%
Polderman, Derks, et al. (2007)	12 (n = 562 twin pairs), cohorts 90–92	SWAN: mother	h^2 90% hyperactivity h^2 82% attention deficit
Genetic studies on executive functions (EF)			
Groot, de Sonneville, Stins, & Boomsma (2004)	5 (n = 237 twin pairs), cohorts 90–92	ANT: EF: Go–No go, sustained attention	h^2 Go–No go (Acc) 0% h^2 sustained attention (RT) ~55%; h^2 Fluctuation sustained attention 0%
Stins, van Baal, Polderman, Verhulst, & Boomsma (2004)	12 (n = 290 twins), cohorts 90–92	Stroop Color Word task Eriksen Flanker task	h^2 Stroop interference 49%; h^2 Flanker effect 0%
Stins et al. (2005)	5 (n = 237 twin pairs), cohorts 90–92	ANT: EF: selective attention, working memory(WM)	h^2 selective attention (RT) 0%; h^2 WM (RT) 54%; h^2 WM (Acc) 0%
Polderman, Stins, et al. (2006)	12 (n = 177 twin pairs + 55 siblings), cohorts 90–92	ANT: WM speed (WMS)WISC–R: WM capacity (WMC) WISC–R: IQ	h^2: WMS 43–51%; h^2: WMC 54–56%; Genetic correlation WMS-WMC partly explained by IQ
Polderman, Gosso, et al. (2006)	5 (n = 237 twin pairs); 12 (n = 177 twin pairs), cohorts 90–92	ANT: EF: selective and sustained attention, WM WISC–R: IQ CBCL: AP scale mother, TRF: AP scale teacher	EF age 5 weak, but AP age 5 strong predictor for IQ age 12; shared genetic factor AP age 5 and IQ age 12
Polderman, Posthuma, et al. (2007)	5 (n = 237 twin pairs); 12 (n = 177 twin pairs), cohorts 90–92	ANT: EF: selective and sustained attention, WM	h^2 (RT) 52–73%; h^2 Slope WM 28–42%; h^2 Fluctuation selective attention 30–59%; stability over time due to genes

Note. AP= attention problems; ADHD = attention deficit/hyperactivity disorder; CBCL = Child Behavior Checklist; h^2 = heritability; Conners = Conners' Rating Scale; TRF = Teacher Report Form; *DSM* = *Diagnostic and Statistical Manual of Mental Disorders*; SWAN = Strengths and Weaknesses of ADHD symptoms and Normal Behavior Scale; ANT = Amsterdam Neuropsychological Tasks; Acc = Accuracy; RT- reaction time; WISC = Wechsler Intelligence Scale for Children.

old, and 18-year old twins, and their younger or older siblings, resulting in data from around 1,200 participants. AP were assessed with a range of widely used checklists, completed by mothers, fathers, teachers, and children themselves. For inhibitory control we used the classical inhibitory control task, the Stroop Color Word task. Psychometric intelligence (IQ) was assessed with the Wechsler Intelligence Scale for Children (WISC; Wechsler et al., 2002) or the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1997).

Method

Participants

Data were available from three independent samples of 9-, 12-, and 18-year-old twins and their siblings (1,209 participants). The twins and siblings took part in different studies; the 9-year-old twins participated in a cognitive MRI study, the 12-year-old twins in a study on attention and cognition, and the 18-year-old twins in

a study on cognition and behavioral problems. All twins were recruited from The Netherlands Twin Register (NTR; Bartels et al., 2007; Boomsma et al., 2006; Boomsma et al., 2008). Siblings of the twins were also invited to participate. Parents and children received an invitation by letter and were subsequently contacted by telephone. None of the participating children suffered from severe physical or mental handicaps. Zygosity of the twins was based on DNA polymorphisms or questionnaire items (Rietveld et al., 2000). Before participation parents and children signed informed consent forms. Studies were approved by the Central Committee on Research Involving Human Subjects and the institutional review board of the VU University Amsterdam. Specific characteristics of each cohort are described below.

9-year-olds. The sample consisted of 112 twin families with an extra sibling ($N = 103$, 59 females) between 9 and 14 years. Twins were born between 1995 and 1996. Mean age of the twins was 9.11 years ($SD = 0.23$), and mean age of the siblings was 11.84 years ($SD = 1.16$). There were 23 monozygotic male twin pairs (MZM), 23 dizygotic male (DZM), 25 MZ female (MZF), 21 DZ female (DZF) and 20 DZ pairs of opposite sex (DOS; van Leeuwen, Van den Berg, & Boomsma, 2008).

12-year-olds. The sample consisted of 177 twin pairs, born between 1990 and 1992, and their siblings ($N = 55$, 26 females). The twins were 12 years old (mean age = 12.42, $SD = 0.16$) and their siblings were between 8 and 14 years of age (mean age = 12.09, $SD = 2.55$). There were 41 MZM, 28 DZM, 56 MZF, 25 DZF, and 27 DOS twin pairs (Polderman, Stins, et al., 2006).

18-year-olds. This group consisted of 186 families of 18-year-old twin pairs (mean age 18.18 years, $SD = 0.21$) born between 1986 and 1989, and their siblings ($n = 101$, 53 females, mean age = 18.43 years, $SD = 3.73$). There were 33 MZM pairs, 34 DZM pairs, 44 MZF pairs, 38 DZF pairs, and 37 DOS twin pairs (Hoekstra, Bartels, & Boomsma, 2007).

Nonresponders. The 12- and 18-year-old twins took part in longitudinal studies that suffered some attrition over time. In the 12-year-old cohort about 75% of the families who participated at age 5, participated again at age 12. The reason for nonresponses was half of the time "no interest without specific reasons," by the children or parents. Other reasons were personal circumstances such as divorce, death, or illness in the family. A small group was no longer registered in the NTR or not attainable by mail or telephone. There were no differences between the nonresponders and responders for AP as reported by the teacher, $F(1, 421) = 1.676$, $p = .196$ or mother, $F(1, 455) = 0.478$, $p = .490$ at age 5, but IQ at that age was higher in responders, $F(1, 472) = 5.685$, $p = .018$. The 18-year-old twins participated for the fifth time. Up to the fourth measurement occasion, the drop-out in the study was low (8%). At the fifth time point, the choice to participate was no longer made by the parents, but by the twins and siblings themselves and participation rate decreased to 58%. For the majority of families, lack of time or difficulties to take leave from work or school were the prime reason to no longer take part. Participants who continued to participate at age 18 had higher mean verbal [$F(1, 205) = 7.834$, $p = .006$] and nonverbal [$F(1, 207) = 4.471$, $p = .036$]. IQ scores at age 5 as compared to participants who did no longer take part when they were 18 years old.

Measures

AP. For the 9-year-old twins AP were assessed with the Child Behavior Checklist (CBCL; Achenbach, 1991a), Teacher's Report Form (TRF, Achenbach, 1991b), and Conners's Rating Scale (CRS–R; Conners, 2001). Data collection is part of ongoing surveys conducted by the NTR every 2 years. For this study data collected at age 7 and 10 were used. The CBCL is a standardized checklist for parents to report the frequency and intensity of behavioral and emotional problems of their children and were filled in by fathers and mothers. The AP scale of the CBCL contains 11 problem items (ranging from 0 = *not true* to 2 = *very often or true*), of which 10 items overlap with the TRF AP scale. Parents are instructed to rate the child's behavior over the last 6 months on a 3-point scale. The TRF AP scale contains 20 problem items, ranging from 0 = *not true* to 2 = *very often or true*. Teachers are instructed to rate the child's behavior over the last 2 months on a 3-point scale, as in the CBCL. The CRS–R is an instrument to assess behavior problems in children and was completed by teachers, fathers, and mothers. The short version contains 28 items that are rated on a 4-point scale, ranging from 0 = *not true at all* to 3 = *very much true*. The problem scale that was used for this study was the index of ADHD scale (see Derks et al., 2006; Hudziak et al., 2005). For the siblings of the 9-year-old twins maternal CBCL and CRS–R data were available, which were completed at the time of the experimental data collection.

In the 12-year-old twins and their siblings, AP were assessed using the same CBCL, Conners, and TRF rating scales. In addition the Strengths and Weaknesses of ADHD symptoms and Normal Behavior Scale (SWAN) was collected. The SWAN (Swanson et al., 2006) comprises 18 items on a 7-point scale (ranging from 1 = *far below average* to 7 = *far above average*) covering two scales, Hyperactivity/Impulsivity and Attention Deficit, which range on a continuum, from severe problems to excellent skills (Polderman, Derks, et al., 2007; Swanson et al., 2006). All children also completed the Youth Self Report (YSR, Achenbach, 1991c). The YSR is a questionnaire based on the CBCL and is completed by children (between ages 11 and 18) themselves. Children are instructed to rate their behavior over the last 6 months on a 3-point scale, ranging from 0 = *not true* to 2 = *very often or true*. The AP scale of the YSR contains 9 problem items, all overlapping with the CBCL and TRF AP scale. All checklists of twins and siblings were completed at the time of the experimental data collection.

For the 18-year-old twins and their siblings YSR data were collected at age 16 and 18. In addition, the Conners's Adult ADHD Rating Scales (CAARS; Conners, Erhardt, & Sparrow, 1999) were filled out by the participants approximately 2 years after the experimental data collection.

Psychometric IQ and Inhibitory Control

The cognitive assessments took place at the VU University. Children were tested in the morning (9- and 12-year old cohort) or afternoon (18-year-old cohort). The twins and siblings from one family were tested simultaneously, in separate rooms by different experienced test administrators. All participants performed a neuropsychological test battery including an IQ test and the Stroop Color Word task. The whole protocol took approximately 3.5 hr (18-year-olds) or 5 hr (9- and 12-year-olds), including breaks. After finishing the assessment, each child received a small present.

All participants of 16 years of age or above completed 11 subtests of the Dutch version of the WAIS–III (Wechsler, 1997). All participants from the 9- and 18-year-old cohort who were younger than 16 years completed the Dutch version of the full WISC–III (Wechsler et al., 2002). In the 12-year-old cohort IQ was assessed with 6 subtests of the Wechsler Intelligence Scale for Children Revised, Dutch version (WISC–R, Van Haasen et al., 1986). Standardized scores of this shortened form of the WISC correlate 0.94 with standardized IQ scores based on all subtests of the WISC–R (Sattler, 1992). Standardization norms were the same across sexes for all IQ tests. All scores were standardized for the appropriate age group, based on population samples of same-aged participants in The Netherlands.

All twins and siblings completed the Stroop Color Word Task (Stroop, 1935). Children had to read aloud three Stroop word-color cards. Each card consisted of 10 rows of 10 items. The first card contained words that were all colors (i.e., "blue," "red," "green," "yellow") printed in black ink. The second card showed small rectangles printed in different colors. The third card displayed names of colors printed in incongruent colors. Children had to name the color of the ink in which the word was printed and not to read the word itself. Performance was assessed as the time (in seconds) to complete each card. Stroop interference was computed as the difference in time between performance of Card 3 and Card 2. Stroop interference is a prototype of inhibitory control, as participants have to inhibit the tendency to produce a dominant or automatic response (i.e., the content of the word instead of the color of the ink).

Analyses

Within each age cohort, all available AP ratings of an individual were used to obtain a standardized AP factor score using maximum likelihood estimation in SPSS (Version 14.0). Thus, the AP factor score in the 9-year-old cohort was based on both mother and father ratings on the AP scale of the CBCL and Conners and on teacher ratings on the AP scale of the TRF and Conners. All these data were assessed at age 7 and at age 10. For the 12-year-old cohort, the AP factor score included mother and father ratings on the AP scale of the CBCL and Conners, teacher ratings on the AP scale of the TRF and Conners, mother-rated SWAN scores, and self-ratings on the AP scale of the YSR. All these date were assessed at age 12. The factor score of the 18-year-old cohort was composed of self ratings on the AP scale of the YSR assessed at age 16 and 18 years, and of self-ratings on the Conners assessed at age 20. Missing observations were replaced using EM imputation methods when at least 25% of possible ratings for an individual were available. Structural equating modeling, as implemented in Mx (Neale, Boker, Xie, & Maes, 2006), was used for the multivariate modeling analyses. Mx provides parameter estimates by maximizing the raw data likelihood, so that all available data, also when some observations for participants are missing, can be included.

Estimates of means, variances, and correlations were obtained from a so-called saturated model. This is a fully parameterized model in which the covariance structure among relatives is allowed to take any value and is not modeled as a function of latent traits such as genetic and environmental factors. The saturated model was fitted to the data of each age cohort in a multigroup analyses distinguishing the data from MZ and DZ twin families. In each cohort-by-zygosity group means and variances of AP, IQ, and Stroop interference were estimated separately for first born twins, for second born twins, and for the siblings. Correlations were estimated in 9×9 correlation matrices (i.e., three traits for the first born twin, for the second born twin, and for the sibling). Correlations were estimated between traits, between twins per trait, between twins and siblings per trait, cross traits between twins (e.g., the correlation between the IQ score of Twin 1 and AP of Twin 2), and cross traits between twins and siblings. Within-person correlations between traits were constrained to be equal across zygosity and in first and second born twins and siblings within each age cohort. The saturated model was used to test whether zygosity, twin-sibling status, sex and age had a significant effect on the means and variances, and we tested whether sex and age effects were the same in each cohort. In addition we tested whether the resemblance within trait and across trait was similar in DZ twins and between twins and siblings.

Finally, we tested whether the correlation between AP and inhibitory control was independent of IQ by fitting the data to a Cholesky factor model with three latent factors: The first factor influenced all three observed variables, the second only AP and Stroop interference, and the last only Stroop interference. In this model the phenotypic variance in all variables and covariance between variables was freely estimated, independent of zygosity and twin-sibling status. We tested whether the covariance between AP and Stroop interference could be constrained to zero, reflecting that all covariance between AP and Stroop interference derived from the first (IQ) factor.

Nested models were evaluated by hierarchic likelihood ratio (chi-square) tests. The chi-square statistic is computed by taking twice the difference between the log-likelihood of the saturated model and the log-likelihood of a sub model with certain constraints (e.g., the constraint that the means are equal for MZ and DZ twins). The associated degrees of freedom are computed as the difference in degrees of freedom between the two hierarchic models (Rijsdijk, 2007).

Genetic Analyses

Male and female data were combined in the MZ twin, DZ twin, and twin-sibling groups in the genetic analyses because there is no evidence for sex differences in heritability for ADHD (Derks et al., 2004; Derks et al., 2007; Hudziak et al., 2005; Rietveld et al., 2003) and IQ (Bartels, Rietveld, van Baal & Boomsma, 2002), and the power to detect sex differences in genetic influences in the independent samples was limited (Polderman, Stins, et al., 2006).

MZ twins share all their genes whereas DZ twins and siblings share on average half of their segregating genes. All twins and siblings grew up in the same family, and thus share their family environment. A first impression of the relative importance of genetic and environmental influences on phenotypic trait variance is obtained by inspecting the (intrapair) MZ correlations and DZ/twin-sibling correlations. MZ correlations twice as high as DZ/twin-sibling correlations indicate genetic influences. DZ correlations higher than half the MZ correlations suggest shared environmental influences, whereas MZ correlations that are of similar magnitude as DZ correlations indicate that only environmental influences play a role (Boomsma, Busjahn, & Peltonen,

2002). The pattern of cross trait correlations of MZ twins and DZ twins/twin-siblings indicates in a similar vein to what extent covariance between traits is influenced by genetic or environmental factors. When cross trait MZ correlations are higher than cross trait DZ/twin-sibling correlations the covariance is likely explained by correlated genetic factors.

Multivariate Model Fitting Procedures

The decomposition of the variance and covariance structures of IQ, AP, and Stroop interference was examined in a nine-variate Cholesky model (three variables for three family members; for an example of the model for one individual see Figure 1). The model decomposes the phenotypic associations between family members and between traits into genetic and environmental contributions to the (co)variance structure, exploiting the known difference in genetic contribution to intrapair MZ and DZ/twin-sibling resemblance. The total variation of each trait and the covariance between traits was decomposed into sources of genetic variance, due to additive genetic effects of different alleles (A), common environmental variance shared by members of a family (C), and unique environmental variance not shared by family members (E). E also includes measurement error. For A, C, and E a factor structure was specified (see Figure 1) that consisted of three factors: The first factor influenced all three observed variables, the second only AP and Stroop interference, and the last only Stroop interference. The factors are correlated within families: A factors are correlated unity in MZ twins and 0.5 in DZ twins and siblings, C factors are correlated unity in all individuals within the same family, and E factors are uncorrelated.

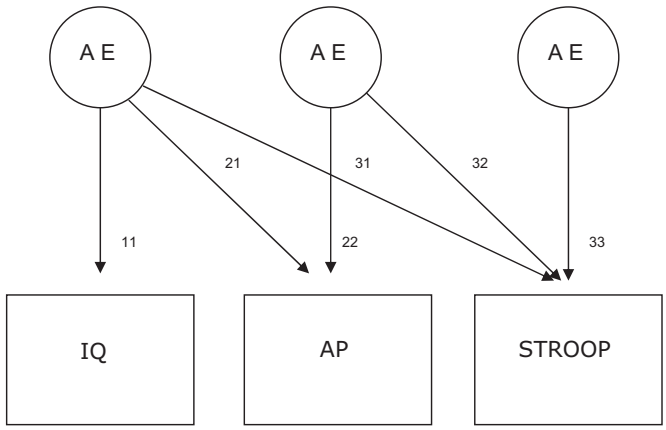
All possible contributions are parameterized in the Cholesky decomposition, and the model serves as a reference model to evaluate the fit of constraints in subsequent models. Constraining the contributions of the latent factors of A or C to be zero provides a test of whether genes (A) or common environment (C) contribute significantly to the total variance and covariance of the data. The significance of the genetic and environmental covariance structure was tested by constraining subsequent pathways in the model at zero. If for example a_{21} could be constrained to zero, this means that genes play no role in the correlation between AP and IQ scores.

To examine the influence of IQ on the covariance between AP and Stroop interference, we estimated the genetic covariance between these traits, independent of IQ. By constraining the genetic covariance between AP and Stroop interference to be zero, reflecting that all genetic covariance derives from the first (IQ) factor, we tested the significance of a genetic covariance unique to AP and Stroop interference. The estimates of the (co)variance matrices can be standardized in genetic and environmental correlations between traits (see formulas below Figure 1). They provide a measure of the extent to which traits are influenced by the same genes or same environmental factors.

Results

Descriptives

The number of twins and siblings in each cohort, and the means and variances of AP, IQ, and Stroop interference are presented in



Factor loadings	a_{11}	a_{21}	a_{31}	a_{22}	a_{32}	a_{33}	e_{11}	e_{21}	e_{31}	e_{22}	e_{32}	e_{33}
Age 9	12.22	-0.21	-2.51	0.79	-0.78	16.17	6.35	-0.05	-3.13	0.47	-1.91	20.06
Age 12	13.41	-0.34	-4.44	0.83	2.07	11.68	6.43	-0.14	-0.19	-0.40	-0.55	12.35
Age 18	8.34	0.03	-4.06	-0.73	0.43	7.28	3.78	-0.11	-0.49	0.67	0.36	8.35

Figure 1. The trivariate Cholesky decomposition for one individual of a family. h^2 IQ is $\frac{a_{11}^2}{a_{11}^2 + e_{11}^2}$. h^2 AP is $\frac{a_{21}^2 + a_{22}^2}{a_{21}^2 + a_{22}^2 + e_{22}^2 + e_{21}^2}$. h^2 Stroop is $\frac{a_{31}^2 + a_{32}^2 + a_{33}^2}{a_{31}^2 + a_{32}^2 + a_{33}^2 + e_{31}^2 + e_{32}^2 + e_{33}^2}$. r_gAP-Stroop is $\frac{a_{22} \times a_{32} + a_{21} \times a_{31}}{\sqrt{a_{21}^2 + a_{22}^2} \times \sqrt{a_{31}^2 + a_{32}^2 + a_{33}^2}}$. r_gAP-Stroop controlling for IQ is $\frac{a_{22} \times a_{32}}{\sqrt{a_{21}^2 + a_{22}^2} \times \sqrt{a_{31}^2 + a_{32}^2 + a_{33}^2}}$.

Table 2. Within each age cohort we tested the effects of sex and age on the means. Sex effects were significant on AP in the 9- and 12-year-old cohort, and these effects were equal across cohorts and zygosity, with boys having more AP (0.36). Other sex effects were present on IQ in the 12-year-old cohort with boys having higher IQ scores (4.62), and on Stroop interference in the 18-year-old cohort with boys having more interference (5.19 ms). Examination of age effects showed a small effect on AP (−0.11) in the 9-year-old cohort, an effect on IQ (1.93) in the 12-year-old cohort, and an effect on Stroop interference in all three cohorts. Age effects were smallest in the 18-year-old cohort (−1.06 ms), and were equal in the 9- and 12-year-old cohort (−4.71 ms).

Sex and age effects on means were included in the subsequent analyses. Means and variances were equal between MZ and DZ twins and siblings for most traits. In the 9-year-old cohort siblings had lower variance on Stroop interference. Testing equality of variances between siblings of the 9-year-old cohort and age-matching twins (12-year-olds) in the multigroup model showed that variance differences were absent in that case. In the 18-year-old cohort siblings had higher variances on Stroop interference and IQ. The variance difference of siblings was modeled in the genetic analyses by using a scalar effect to account for their variance, assuming that the components of genetic and environmental variance were proportional to those observed in the twins.

Correlations Among IQ, AP, and Stroop Interference

The phenotypic correlations among AP, Stroop interference, and IQ are shown in Table 4. In the 9- and 12-year-old cohort IQ had a negative correlation with AP, but in the 18-year-old cohort this correlation was absent ($r = -0.26$, -0.34, and -0.04, respectively). IQ and Stroop interference showed a more consistent pattern; children with higher IQ scores had less Stroop interference in each cohort, this association increased with age, with correlations in each cohort of $r = -0.16$ (CI: $-.28$ to $-.04$), -0.24 (CI: $-.33$ to $-.12$) and -0.35 (CI: $-.43$ to $-.25$), respectively. In the 9- and 18-year-old cohorts correlations between AP and Stroop interference were small and nonsignificant ($r < 0.08$). A correlation of 0.18 was found between AP and Stroop interference in the 12-year-old cohort (more AP are associated with more Stroop interference). When we corrected for IQ the correlation between AP and Stroop interference decreased to 0.09 and was no longer significant.

Table 2
Number of Twins and Siblings, Means, and Variances of Attention Problems (AP), IQ, and Stroop Interference, Per Age Cohort

Variable	AP	IQ	Stroop
9-year-old cohort			
First-born twins *n*	87	113	103
Second-born twins *n*	87	113	112
Siblings *n*	93	100	99
Total *N*	267	326	314
M	0.004	101.895	64.296
SD	0.970	14.747	26.247
Range	−1.19 to 3.71	64 to 150	18 to 160
12-year-old cohort			
First-born twins *n*	171	176	171
Second-born twins *n*	173	177	169
Siblings *n*	53	52	50
Total *N*	397	405	390
M	0.000	99.814	48.341
SD	0.966	15.200	18.341
Range	−1.44 to 5.20	55 to 143	3 to 119
18-year-old cohort			
First-born twins *n*	191	181	182
Second-born twins *n*	188	183	182
Siblings *n*	91	80	79
Total *N*	470	444	443
M	0.004	102.043	30.164
SD	1.002	10.384	13.767
Range	−2.38 to 4.17	60 to 134	6 to 107

Twin-sibling correlations were not significantly different from DZ correlations in any of the three cohorts, $\chi^2(12) = 18.585$, $p = .099$; $\chi^2(12) = 7.596$, $p = .816$; and $\chi^2(12) = 17.316$, $p = .138$, respectively. The diagonal of Table 3 displays the twin/twin-sibling correlations for all variables in each age cohort. MZ correlations were higher than the DZ/twin-sibling correlations on all variables, therefore the genetic models contained latent factors for A, C, and E. Based on the results of the saturated model fitting, age and sex were included as covariates. Table 3 also shows the cross trait correlations between MZ and DZ/twin siblings. MZ correlations were higher than DZ/twin-sibling correlations for AP and IQ in the 9- and 12-year-old cohort, between AP and Stroop interference in the 12-year-old cohort, and between IQ and Stroop interference in the 12- and 18-year-old cohort.

Multivariate Genetic Analyses of IQ, AP, and Stroop Interference

In all age cohorts the contribution of C could be dropped from the ACE model, $\chi^2(6) = 9.072$, $p = .170$; $\chi^2(6) = 2.146$, $p = .906$; and $\chi^2(6) = 2.019$, $p = .918$, respectively. Factor loadings from the AE models are shown below Figure 1. The heritability estimate of Stroop interference was 39% in the 9-year-old cohort, and 51% in the older cohorts. The relative contribution of genetic variance on AP was high in both younger cohorts (heritability of 74% and 82%, respectively), and moderate in the 18-year-old cohort (54%). Variation in IQ was to a large extent explained by genetic factors; 75%, 81%, and 83% in the 9-, 12-, and 18-year-old cohort, respectively.

We tested the significance of genetic and environmental contributions to the covariance among traits by constraining respective path loadings from the AE model to zero. Significant genetic covariances were present between IQ and AP in the 9- and 12-year-olds (standardized genetic covariances, $r_g = -0.26$ and -0.38, respectively), and between IQ and Stroop interference in the 12- and 18-year olds ($r_g = -0.35$ and -0.50, respectively). One unique environmental covariance was significant namely between AP and IQ in the 12-year-old cohort ($r_e = -0.32$). Full results for the genetic and unique environmental correlation structure are given in Table 4.

The genetic correlation between AP and Stroop interference was 0.28 the 12-year-old cohort, but nonsignificant, $\chi^2(1) = 2.566$, $p = .109$. Inspection of the factor loadings (Figure 1 footnote) shows that this genetic correlation derives entirely from the genes influencing all three variables, that is, genes shared by AP and Stroop interference with IQ. The genetic correlation based on genetic factors influencing only AP and Stroop interference was 0.15.

Table 3
Twin Correlations on the Diagonal (MZ/DZ-Twin-Sibling), and Cross Trait Correlationsof Attention Problems (AP), IQ, and Stroop Interference Per Age Cohort

	AP	IQ	Stroop
Age 9			
AP	.83/.36	−.14	.06
IQ	−.20	.75/.56	−.13
Stroop	.04	−.07	.33/.24
Age 12			
AP	.81/.14	−.03	−.02
IQ	−.28	.83/.38	−.13
Stroop	.18	−.22	.54/.16
Age 18			
AP	.51/.27	−.08	.02
IQ	.04	.82/.44	−.21
Stroop	−.03	−.31	.56/.20

Note. MZ is shown below the diagonal and DZ-twin-sibling is shown above the diagonal. MZ = monozygotic twin pairs; DZ = dizygotic twin pairs; AP = attention problems.

Discussion

The current study investigated the association between AP and inhibitory control across childhood in three relatively large cohorts of twins, aged 9, 12, and 18 years old, and their singleton siblings. The use of family data offered the opportunity to investigate the genetic correlation between AP and inhibitory control. The additional measurement of IQ allowed us to test whether there is a set of genetic factors that affect AP and inhibitory control, independent of general cognitive ability. Inhibitory control was found to be heritable in the 9-, 12-, and 18-year-old cohorts (36%, 51%, 51%), confirming earlier studies on the heritability of Stroop interference (Stins et al., 2004) in a subsample of the 12-year-olds, and in an independent sample of young adults (Friedman et al., 2008). The expected phenotypic and genetic correlations between inhibitory control and AP were only found in the 12-year-old cohort. Moreover, these correlations derived from (genetic) factors that were shared with IQ, and no evidence was found for a set of genetic factors specific to AP and inhibitory control only. As a new finding this study reports significant phenotypic and genetic correlations between IQ and inhibitory control across childhood.

The prominent correlation between IQ and AP in children of the 9- and 12-year-old cohorts confirmed previous studies on the association between AP and IQ. Friedman et al. (2007) investigated a large population cohort the association between AP at several time points during childhood (age 7 to 14) and IQ scores at age 16, reported longitudinal correlations between −0.21 and −0.27. Polderman, Gosso, et al. (2006) reported somewhat higher correlations between AP measured by both teachers and parents at age 5 and IQ scores at age 12 (−0.30/−0.31), although Kuntsi et al. (2004) found a correlation of −0.30 between IQ scores and AP in 5-year-old children. Thus, the association between AP and intelligence is negative and rather stable during childhood. In keeping, the correlations between AP and IQ were to a large extent explained by shared genes. Similar findings were reported by Kuntsi et al. (2004) and Polderman, Gosso, et al. (2006) who found that the association between AP and IQ scores in 5-year-old twins also was explained by shared genetic factors. Moreover, previous research in the 12-year-old cohort showed a longitudinal genetic association during childhood between AP and IQ scores (Polderman, Gosso, et al., 2006). It thus seems that across childhood, a same set of genes has an influence on AP and IQ performance. The genetic correlation between IQ and AP may apply to IQ and ADHD too as the latter is part of the continuum of AP (Hay et al., 2006; Kuntsi et al., 2005; Levy et al., 1997; Polderman, Derks, et al., 2007), and AP and ADHD have a large genetic overlap (Derks et al., 2008).

The significant association between AP and IQ had disappeared in the adolescence cohort (18 years old). This might be due to the use of self-reported AP scores in the oldest cohort, instead of the parental or teacher ratings used in the younger cohorts. Alternatively, participants of this age may have acquired skills to regulate their impairing behavior, and attenuate the effects of their attention deficits on IQ test performance. For example, some evidence suggests that symptoms of hyperactivity and impulsivity may wane with increasing age (Biederman, Mick, & Faraone, 2000).

Taken together, these results suggest that differences in inhibitory control between ADHD and control children originate from (genetic) factors that are shared with IQ and argue against the use of inhibitory control as a specific endophenotype for AP in children. It would be interesting to repeat the current analyses using other well-known and widely used inhibition designs, like the Go–No go task (Slaats-Willemse et al., 2003), or stop signal task (Rommelse et al., 2008). These would reveal how vigorous the association between IQ and inhibitory control actually is and check the robustness of the influence of IQ on the association between AP and inhibitory control. As it stands, previous suggestions that working memory, selective and sustained attention (Polderman, Posthuma, et al., 2007), or other executive functions (Rommelse, 2008) could be used as potential endophenotypes may need to be reconsidered. The genetic association between IQ and inhibitory control makes inhibitory control a plausible endophenotype for IQ, rather than for AP.

A possible explanation for the genetic correlations among AP, IQ, and inhibitory control is provided by the "generalist genes" hypothesis that assumes that most genetic effects on cognitive (dys)functions are

Table 4
Phenotypic (r_P), Genetic (r_G), and Unique Environmental (r_E) Correlations Among Attention Problems, IQ and Stroop Interference Per Age Cohort

	AP	IQ	Stroop
Age 9			
AP	1		
IQ	−0.26*/−0.26*/−0.12	1	
Stroop	0.07/0.09/−0.09	−0.16*/−0.15/−0.15	1
Age 12			
AP	1		
IQ	−0.34*/−0.38*/−0.32*	1	
Stroop	0.18[a]/0.28[b]/0.05	−0.24*/−0.35*/−0.02	1
Age 18			
AP	1		
IQ	−0.04/0.06/−0.15	1	
Stroop	0.01/−0.08/0.05	−0.35*/−0.50*/0.00	1

[a] 0.09 after controlling for IQ. [b] 0.15 after controlling for IQ.
* $p < .05$.

general rather than specific (Kovas & Plomin, 2006). Consequently, genes affecting general cognitive functioning—like IQ—are largely the same genes that have an effect on more specific cognitive abilities. Candidates that could fulfill the role of generalist genes are likely involved in the dopaminergic pathways of the brain as it is believed that this system plays a major role in ADHD (Castellanos & Tannock, 2002; Durston, Mulder, Casey, Ziermans, & van Engeland, 2006) and cognitive functioning (Nieoullon, 2002). Mill et al. (2006) tested whether the DRD4 seven-repeat allele and the DAT1 10-repeat allele were associated with variation in intelligence among children with ADHD. They found evidence for this association in two independent samples, from New Zealand and the United Kingdom. An attempt to replicate these findings in three larger, independent Brazilian samples by Genro et al. (2006) failed. In the 12-year-old cohort three genes have been identified in relation to IQ performance. These were CHRM2 (Gosso, De Geus, Polderman, Boomsma, et al., 2007), COMT (Gosso et al., 2008), and SNAP-25 (Gosso, De Geus, Polderman, Heutink, et al., 2008). Variants in the latter gene have already been found to be associated with ADHD (Barr et al., 2000; Brophy, Hawi, Kirley, Fitzgerald, & Gill, 2002; Feng et al., 2005) but the variant of SNAP-25 that was associated with IQ in the 12-year-old cohort (i.e., rs363050) showed no association with AP. In addition to the genetic correlations we also found significant unique environmental influences for the association between AP and IQ ($r_e = -.32$) in the 12-year-old cohort and correlations in the same directions, but nonsignificant, in the other cohorts. Possible unique environmental factors include pre- or postnatal complications, a serious accident, or a severe illness, that affect one child and not his or her sibling. Lehn et al. (2007) investigated unique environmental influences on AP and ADHD in a group of concordant (i.e., similar) and discordant (i.e., dissimilar) Dutch MZ twin pairs on these traits. Because MZ twins share all their genes, differences between them must result from environmental influences. The affected twins of discordant pairs in the study of Lehn et al. had lower birth weights and were disadvantaged in terms of maturation. It has been shown previously that low birth weight might be a risk factor for cognitive development and ADHD (Bhutta, Cleves, Casey, Cradock, & Anand, 2002).

In summary, in three large age cohorts of twins and siblings we found no evidence for a phenotypic or genetic correlation between AP and inhibitory control, adding new doubts to the assumption of a crucial etiologic role of impaired inhibition in children with AP. A new finding was the robust association between IQ and inhibitory control in all cohorts, and the significant influence of IQ on the association between AP and inhibitory control, suggesting that IQ might explain a part of the association between AP and inhibitory control as reported in the literature. Given that IQ is an important predictor of educational achievement (Duncan et al., 2007), socioeconomic status later in life, and health in adulthood (Huisman, Kunst, & Mackenbach, 2005) the association of AP to low general cognitive ability is an important direction of research for the future.

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